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Compulsivity in Opioid Dependence

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ABSTRACT

Objective: This study aimed to investigate the relationship between compulsivity versus impulsivity and structural MRI abnormalities in opioid dependence.

Method: We recruited 146 participants: i) patients with a history of opioid dependence due to chronic heroin use (n=24), ii) heroin users stabilised on methadone maintenance treatment (n=48), iii) abstinent participants with a history of opioid dependence due to heroin use (n=24) and iv) healthy controls (n=50). Compulsivity was measured using Intra/Extra-Dimensional (IED) Task and impulsivity was measured using the Cambridge Gambling Task (CGT). Structural Magnetic Resonance Imaging (MRI) data were also obtained.

Results: As hypothesised, compulsivity was negatively associated with impulsivity ($p<0.02$). Testing for the neural substrates of compulsivity versus impulsivity, we found a higher compulsivity/impulsivity ratio associated with significantly decreased white matter adjacent to the nucleus accumbens, bed nucleus of stria terminalis and rostral cingulate in the abstinent group, compared to the other opioid dependent groups. In addition, self-reported duration of opioid exposure correlated negatively with bilateral globus pallidus grey matter reductions.

Conclusion: Our findings are consistent with Volkow & Koob's addiction models and underline the important role of compulsivity versus impulsivity in opioid dependence. Our results have implications for the treatment of opioid dependence supporting the assertion of different behavioural and biological phenotypes in the opioid dependence and abstinence syndromes.

Significant Outcomes:

- Both heroin users and short-term abstinent participants made significantly more errors on the compulsivity (IED) task than healthy controls.
- Brain structure abnormalities associated with compulsivity versus impulsivity were identified.
- Compulsivity was negatively associated with impulsivity and the ratio of compulsivity/impulsivity was inversely related to nucleus accumbens, and bed nucleus of stria terminalis white matter integrity.

Limitations

- We cannot address causal effects due to the cross-sectional design of the current study.
- The findings may not be generalised to female populations as we recruited only treatment-seeking male individuals.

Abbreviations:

ABS: Abstinent group
ANOVA: Analysis of Variance
ANCOVA: Analysis of Covariance
BNST: Bed Nucleus of Stria Terminalis
CGT: Cambridge Gambling Task
IED: Intra/Extra-dimensional,
H: Heroin group
HC: Healthy Control group
MMT: Methadone Maintenance Treatment group
MRI: Magnetic Resonance Imaging
SPM: Statistical Parametric Mapping

Introduction

Volkow & Koob (2016) described drug addiction as a disorder that progresses from impulsivity to compulsivity characterised by maladaptive behaviour to obtain and consume more drugs at the expense of health and social interactions [1]. Chronic exposure to opioids occurs frequently in both therapeutic pain and substance misuse populations [2]. Methadone Maintenance Therapy (MMT) represents a dominant treatment intervention for a substantial number of people who become dependent on chronic illicit opioid use such as heroin [3,4]. From the range of studies that have examined the impact of methadone on neuropsychological functioning, there seems to be an evidence base describing impairment in methadone users in a number of neuropsychological domains [5]. Studies which have compared methadone users with abstinent ex-heroin dependent and substance free healthy controls have indicated that the abstinent ex-heroin dependent group performed at a superior level to methadone users but below the level of substance free and healthy controls [5]. For example Darke *et al* (2012) compared cognitive domains in 125 current opioid users, 50 abstinent and 50 healthy controls. They concluded that current opioid users have a poorer performance on some tests compared to abstinent and control groups [6]**.**

This suggests that neuropsychological deficits observed in opioid users may be subject to at least partial recovery with total withdrawal from opioids, but that some permanent damage may occur. However, interpretation of these results must be be done with caution, as there were a number of possible causes of neuropsychological dysfunction in this population. These include the pre-drug misuse traits in people who go on to become dependendent on opioid drugs, traits associated with dependent individuals who achiece abstainence, as well as effects of the drug itself and any other illicit or prescribed substances, alcohol abuse, head injury, overdose, or comorbid psychiatric disorders. Unfortunately it is difficult to address traits without a longitudinal study and each possible confounding variable is common in the opioid dependent population. It is therefore likely that factors other than the direct effects of methadone account for at least some of the wide range of deficits observed in the clinical research literature [2,7].

Previously we reported that patients on MMT and others still taking illicit heroin exhibited heightened impulsivity [7,8]. This was supported by our previous meta-analysis suggesting robust impairment in cognitive impulsivity (risk taking) with a moderate effect size of 0.70 ($p<0.01$) [2]. In contrast to studies on impulsivity, there are far fewer studies on compulsivity [9] and none to our knowledge on abstinent former opioid users which include use of structural Magnetic Resonance Imaging (MRI).

Robbins *et al* (2012) argued that impulsivity and compulsivity are cognitive endophenotypes with impulsivity relevant for initiating actions, whereas compulsivity is more linked with terminating actions [9]. In addition, Meunier *et al* (2012) and Ersche *et al* (2011) linked compulsivity to orbitofrontal cortex [10,11]. Friedman *et al* (2000) compared opioid symptoms to Obsessive Compulsive Disorder (OCD) [12]. These authors concluded that the level of compulsivity and obsessionality in opioid dependence is similar to OCD and alcohol addiction, and rituals were inversely related to the number of relapses during opioid rehabilitation, being positively correlated with non-drug OCD symptoms.

Previous neuroimaging studies have reported abnormal brain structure in opioid users [6,13] with compulsive behaviour linked to abnormalities in the orbitofrontal cortex and striatum [10,11]**.** Intra/Extra-Dimensional task (a neurocognitive task that measures compulsivity) conducted studies have confirmed a preferential role for dopamine in non-opioid-dependent-heroin-using patients [14-17], particularly in the ventral striatum, an important part of the brain reward circuitry. In this context, low dopamine tone might be a plausible neurobiological mechanism contributing to opioid dependence [1]. However, previous behavioural and neuroimaging studies investigating this question have generated inconsistent results [18]. Changes in both compulsivity and impulsivity have been linked to functional changes in brain regions such as the extended amygdala (central nucleus of amygdala and bed nucleus stria terminalis) and the shell of the nucleus accumbens, both of which receive dense dopaminergic innervation [8]. Holander and Wong proposed an impulsive-compulsive diathesis model with impulsivity and

compulsivity at the opposite ends of a single dimension, implying a negative correlation between impulsivity and compulsivity measures [19]. In contrast Fineberg and colleagues proposed that the two constructs may be considered as endophenotypes representing *uncorrelated* factors: i.e. a characteristic tendency to reward-seeking behaviour (impulsivity) and an uncorrelated drive to avoid punishment (compulsivity) [20].

Impulsivity and compulsivity constructs have similarities and differences [9,12]. To address the above issues, we aimed to identify brain structure abnormalities more linked to compulsivity than impulsivity, by testing for correlations between grey and white matter probability and the ratio of compulsivity/impulsivity measures.

We predicted impairment in compulsivity in three groups of opioid dependent patients when compared to the healthy control group. Second, we predicted the extent of these impairments would correlate with impulsivity. Specifically, we investigated a possible association between caudate nucleus and orbitofrontal cortex structure with compulsivity measures relative to impulsivity measures in opioid dependence. Finally, based on previous studies [23,24], we predicted that behavioural impairment would be associated with the duration of exposure to chronic opioid usage.

Material and Methods

The study was approved by the local Research Ethics Committee (REC Reference Number 06/S1401/32)

Study 1 (Neurocognition)

Study samples

One hundred and forty-six male participants were recruited into four groups; opioid dependent and daily illicit chronic heroin (H) group (n=24), opioid dependent chronic methadone maintenance (MMT) group (n=48), formerly opioid dependent and currently abstinent (ABS) group (n=24) and non opioid dependent healthy control (HC) group (n=50). The ABS group had a history of chronic opioid use of more than three years and were objectively free from all opioids and other psychoactive substances between six and twenty weeks

after a period of rehabilitation. Diagnoses were made according to the Mini International Neuropsychiatric Interview (MINIPlus v. 5.0) [25]. Detailed drug histories and relevant demographic data were acquired prior to testing by one of the authors (AB). At the time of testing, no participants experienced clinical opioid withdrawal symptoms or presented with features of intoxication. The Clinical Opiate Withdrawal scale (COWS) was used to quantify the level of opioid withdrawal [26]. Current and premorbid intelligence was estimated using the Wechsler Abbreviated Scale of Intelligence (WASI) and National Adult Reading Test (NART) [27] respectively. The Fagerström test for Nicotine Dependence [28] was used to quantify nicotine dependence. All individuals were right handed. Exclusion criteria for all groups were: past or current histories of psychotic disorder, post-traumatic stress disorder, neurological and neurodevelopmental disorders, head injury, confirmed history of non-fatal overdose episodes requiring hospitalisation, diagnoses of antisocial and borderline personality disorder and presence of co-occurring benzodiazepine, stimulant and/or alcohol dependence. By the time individuals consented into this study none were subsequently excluded and they completed all tests.The screening and diagnostic tests used in this study are reported in **Supplementary Table 1**.

Compulsivity and Impulsivity

Each participant was assessed by an experienced and trained senior clinical nurse using the Intra-Extra Dimensional (IED) set shifting task and Cambridge Gambling Task (CGT) from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (www.cambridgecognition.com), which assessed compulsivity and impulsivity respectively [7, 20-23]. In a recent review, Fineberg and colleagues proposed that the CGT measures 'cognitive impulsivity' and quality of decision-making and the IED measures compulsivity and 'cognitive inflexibility' [20]. Consistent with the literature, we used the following outcome measures as indices of cognitive impulsivity derived from the CGT: quality of decision-making, risk taking, deliberation time, delay aversion and risk adjustment [7,8,20]. Compulsivity measures include pre-ED errors, EDS errors and total errors. Total errors and total trials (adjusted) variables report the total number of errors with an adjustment for the stages

not attempted due to previous failure. We chose these variables because our previous meta-analysis highlighted abnormalities in these measures [7]. All participants were tested with the same neuropsychological test battery in a fixed order.

Statistical analysis

Data were analysed using ANOVA and ANCOVA. Nonparametric tests were used when data did not meet the assumptions of normality and homogeneity of variance. ANOVA was used to test for group differences. To control for family-wise error we used *post-hoc* Bonferroni-corrected pairwise comparisons. After correction, results with $p<0.05$ were considered significant. ANCOVA was used to test for removing the effect of covariate factors: pre-morbid IQ and age. Effect sizes were calculated using Cohen's *d* statistics. Analyses were conducted using SPSS v20 (SPSS IBM, USA).

Study 2 (Neuroimaging)

Participants

A representative subset of the participants from Study 1 took part in Study 2. From the overall group we tested a total of seventy-one individuals: MMT group (n=33), ABS group (n=15) and HC group (n=23).

Scanning

T_1 weighted images were acquired with a voxel size 0.8x0.8x1.0 mm with whole brain coverage, TR 1.9 sec and TE 2.64 ms using a Siemens 3T Trio. An experienced Consultant Radiologist reported any incidental findings.

Image analyses

Voxel based morphometry (VBM) was done using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/) [29]. For pre-processing, T_1 weighted images for each participant were segmented into grey and white matter probability maps, spatially normalised with modulation to preserve the total amount of matter and smoothed with an 8mm Gaussian kernel [30]. T-tests

were used to test the null hypothesis of no difference between patient groups and controls.

We tested for significant reductions in grey and white matter in methadone and abstinent groups relative to controls. Correlation analyses were used to test the null hypotheses of no relation between white matter and grey matter measures with IED behavioural measures, ratio of IED/CGT behavioural measures (reflecting the relative effect of compulsivity to impulsivity), and self-report duration of opioid exposure as years. The threshold of significance was defined as $p<0.05$ at a whole brain corrected level using a popular Monte Carlo technique [31] (http://www2.bc.edu/~slotnics/scripts.htm). Brain regions were identified by converting Montreal Neurological Institute coordinates into Talairach coordinates using the Yale conversion calculation (http://bioimagesuite.yale.edu/mni2tal/index.aspx) and inspection of the Talairach Atlas [32].

Results

Demographics

There were no significant differences between patient groups with respect to clinical characteristics such as age of first heroin use, years of opioid use, methadone dose and severity of nicotine dependence. The mean age for the H group was 26.3 years for the MMT group was 30.2 years for the ABS group was 36.6 years and for the healthy control (HC) group 28 years. The ABS group was on average significantly older than the HC group in the first study. However, in the second study the four groups were well matched with respect to handedness, gender, nicotine dependence and age. The pre morbid IQ scores were significantly different in the ABS groups when compared with the HC group. **Table 1** summarises the characteristics for the three opioid dependent groups and HC group.

Study 1: **Behavioral effects of heroin, methadone and abstinence on compulsivity and impulsivity**

There was no significant effect of group on EDS error, [F = (3,126) = 1.7, p=0.2] with the ABS group making more errors than the HC goup [t = 2.5, p=0.045]. For total errors there was a significant effect of group [F = (3,140) = 2.5, p=0.05], with the ABS [t = 3.1, p<0.001] and H [t = 1.3, p<0.001] groups making more errors than the HC group. There was a significant effect of group on total error adjusted [F = (3,145) = 3.2, p=0.026] with the ABS and H groups making more errors than the HC group [t = 3, p=0.009], [t=2.7, p=0.008]. For stages completed there was a significant effect of group [F = (3,145) = 2.99, p=0.033] with the HC group completing more stages than the ABS [t=3, p=0.01] and the H groups [t=-2.4, p=0.02]. There was a significant effect of group [F = (3, 121) = 2.8, p=0.043] with the ABS group [t=3.2, p=0.006] and the H group [t=2.8, p=0.007] adjusting for more trials than the HC group. There was a significant effect of group on pre-ED errors [F = (3,126) = 2.6, p=0.05] with the H group making more errors than the HC group [t=3.1, p=0.003]. There was no significant effect of group on completed stage errors [F = (3, 145) = 0.4, p=0.7], completed stage trials [F = (3, 118) = 0.4, p=0.8], total trails [F = (3, 99) = 0.4, p=0.8] and completed stages errors [F = (3, 145) = 0.3, p=0.8]. In summary, the ABS and H groups made more errors in the IED task than the HC group as shown in Figure 1. **Table 2** summarises the IED task findings. The CGT findings are reported in the **Supplementary Table 2.**

Correlations with compulsivity / impulsivity ratio

A significant negative correlation between compulsivity and impulsivity measures [beta= -0.019, t= -2.3, p=0.02] was found across all opioid dependent groups. In the patient group alone we found that greater impairment in compulsivity total error (IED) was negatively associated with increased risk adjustment (CGT) [beta= -0.24, t= -2.28, p=0.03]. This association was also observed between the quality of decision-making (CGT) and pre-ED errors [beta= -0.25, t= -2.3, p=0.03]. A parallel analysis was performed only with the H Group and a significant effect found [beta= -0.043,

t= -3.4, p=0.001], also for pre-ED errors and quality of decision making showing that cognitive inflexibility and impulsivity were negatively correlated in opioid dependent participants. In addition, we found a significant association between self-report years of opioid misuse and compulsivity (EDS error) [beta= -0.37, t= -2.05, p=0.05]) and impulsivity (quality of decision making) [beta= 0.5, t= 3.2, p=0.004] and overall proportion of bet in the CGT [beta= 0.38, t= 2.19, p=0.04]) (**Figure 1**).

Study 2: **Correlations with brain structure and compulsivity/impulsivity ratio and opioid exposure**

Figure 2 shows that a greater compulsivity/impulsivity ratio was associated in the ABS group with significantly decreased white matter in the nucleus accumbens (0, 16 -12), in the bed nucleus of stria terminalis (10, 2, -12) and in the rostral cingulate (6, 38, 6). In the MMT group we found that compulsivity/impulsivity ratio correlated negatively with amygdala (-32, -8, -10), striatum (-2, 0, 0) and orbitofrontal cortex (2, 54, -2) white and grey matter values. With opioid exposure we found a negative correlation with bilateral globus pallidus grey matter (14, 0, -2; -16, -4, 0).

Correlations with brain structure and compulsivity measures

Increased total error adjusted correlated negatively with subgenual cingulate cortex (-14, 24, -12), anterior cingulate cortex (-20, 2, 34), dorsolateral prefrontal cortex (42, 30, 12), and ventral tegmental area (-4, -18, -6) grey matter. More total errors on the IED task was associated with decreased grey matter probability in the ventral tegmental area (-4, -20, -4), medio-prefrontal cortex (-12, 48, 0) and periaqueductal grey (-10, -36, -18). Increased pre-ED errors were associated with significantly decreased white matter in the anterior cingulate cortex: (-2, 8, 40), bilateral insula (44, 6, -14; -42, 4, -10) and nucleus accumens septi area (0, 12, 2). Increased EDS errors in the ABS group correlated negatively with orbitofrontal cortex (34, 58, -8), prefrontal cortex (20, 66, 12) white matter probability.

Discussion

On the basis of Volkow & Koob's concept of addiction, it has been proposed that impulsivity dominates in the early stages of addiction, whereas compulsivity dominates in the later stages [4]. The present study therefore investigated whether compulsivity and impulsivity reflected opposite ends of a single dimension in opioid dependent subjects using IED and CGT behavioural measures and structural MRI.

Both H and ABS groups were impaired in compulsivity measures as previously reported for H users [23]. As hypothesised, we also found that increased compulsivity correlated with decreased impulsivity. Compared to the HC group, the H and ABS groups made substantially more errors on the IED task. In the present study compulsivity and impulsivity performance was positively associated with years of opioid exposure, suggestive of a cumulative process associated with prolonged opioid misuse. The ABS group had a significant reduction in white matter in the dorsolateral prefrontal cortex, ventricles and posterior cingulate cortex relative to healthy controls. In contrast, the MMT participants had thalamic and prefrontal cortex white matter reductions. Variation in the compulsivity/impulsivity ratio correlated with amygdala and striatal grey matter reductions. A correlation analysis revealed that opioid exposure also correlated negatively with globus pallidus grey matter.

Previous studies have suggested that the need to keep taking drugs to avoid a withdrawal syndrome (impulsivity) and the intense drug craving (compulsivity) are inseparable cognitive endophenotypes [9]. However we believe that our results are consistent with Holander and Wong's alternative proposal of the compulsive-impulsive diathesis model, with impulsivity and compulsivity at the opposite ends of a single dimension [19]. Impaired set-shifting has been found in the short-term ABS and H groups but not in the MMT group. Such reversal-learning/set-shifting impairments have been linked to dysfunction of serotonin in the OFC [33,34] and dysfunction of dopamine in the striatum [35]. It might be that methadone treatment helped in rescuing behavioural flexibility via normalisation of the OFC serotoninergic tone, which

was then impaired after methadone cessation. However due to the cross-sectional design of the current study we cannot address causal effects.

Our findings provide compelling evidence that the ABS group were impaired on compulsivity measures. We also found a negative correlation between compulsivity and impulsivity measures. The variables (a) total errors (IED) and pre-ED errors for compulsivity, and (b) risk adjustment and quality of decision making for impulsivity, were the relevant variables in the linear regression models. These findings suggest that there are differential cognitive impairments relative to the different stages of the addiction cycle.–We also found evidence for abnormal brain structure: ABS and MMT groups exhibited white matter reductions relative to the HC group. The ABS group additionally had grey matter reduction in dorsolateral prefrontal cortex, ventricles and posterior cingulate. Notably the prefrontal cortex is linked to IED set-shifting's impairments in non-human primates [36] and humans [37]. Significant decreases in white matter were found in the MMT group in medial prefrontal cortex and anterior cingulate cortex. These structures have been implicated in the regulation of rewards, emotions and decision-making [1]. The medial prefrontal cortex plays a critical role in decision-making, such as conflict monitoring [38], error detection [39], and adaptive and emotional responses,[40, 41] **with t**he anterior cingulate cortex being activated during negative affect and cognitive control [42].

The ABS group also exhibited white matter reductions adjacent to the insula and subcortical (nucleus accumbens and ventral tegmental area) structures with increased EDS errors. Notably, the insula has been implicated in craving for opioid dependence [24].

Robbins and colleagues proposed that both compulsivity and impulsivity are linked to abnormal striatal and prefrontal cortex functioning [9]. Consistent with this, we found the compulsivity/impulsivity ratio was associated with nucleus accumbens/striatal structural reductions in the ABS group and orbitofrontal cortex in the MMT group. Abnormal globus pallidus structure is associated with heroin intoxication [43] and is strongly associated with motor impairments [44] associated with impulsivity (risk adjustment) and methadone dose [8]. Our study found grey matter reductions in globus pallidus associated with duration of exposure to opioids. Interestingly both

impulsivity and compulsivity measures were correlated with increasing years of opioid abuse suggesting a cumulative effect of opioid use.

In summary, short term opioid abstinence was associated with persistent compulsivity related impairments and associated brain structural abnormalities. To establish a possible clinical endophenotype of abstinence, a longitudinal study is required.

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